Pulmonary Alveolar Proteinosis

Review of the Literature with Follow-up Studies and Report of Two New Cases

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■ *In the period from 1958, when Rosen and coworkers first reported a condition in which the pulmonary alveoli are filled with an eosinophilic material, to the beginning of 1964, reports of 93 cases had accumulated in the world literature, including two cases included herein. The cause of this disease, which Rosen called "pulmonary alveolar proteinosis," is not known, nor is there a known means of cure.*

The usual patient is a white man between 30 and 50 years of age who may do any kind of work. The first symptoms may be those of pulmonary infection or pulmonary insufficiency. Patients with pulmonary alveolar proteinosis are prone to nocardiosis and infection with other fungi. Diagnosis is made by lung biopsy.

Twenty of the 93 patients reported upon were alive at the time of this review, 37 were dead and 36 had been lost to follow-up.

IN 1953, Linell and coworkers[56] reported a 57-year-old joiner who had begun to have easy fatigability and a mild, slightly productive cough six years before his death. At the onset of these symptoms, x-ray films of the chest showed densities in both lower lung fields, and these abnormalities persisted through the years. About a year before he died, facial pustules developed and *Cryptococcus neoformans* grew on cultures of material from them. This organism was also cultured from the spinal fluid, the blood and material washed from the stomach. At autopsy destruction of the right lower lobe of the lung by masses of cryptococci was observed. On examination of the pneumonia-like foci in the left lung, unusual microscopic features were noted which were not epithetically described until Rosen in 1958 used the term *pulmonary alveolar proteinosis.*

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As chief of the Pulmonary, Mediastinal and Ear, Nose and Throat Pathology Section of the Armed Forces Institute of Pathology, Rosen had received from puzzled pathologists throughout the country 16 different biopsy specimens of lung tissue in which these characteristics were present. Then Castleman at Harvard Medical School reported four similar cases and Liebow of Yale added seven, making a total of 27 patients in whom the particular pathological features termed pulmonary alveolar proteinosis were reported to have been observed.

To the question, "Could this disease have been overlooked by pathologists until recently?", pathologists answer that the microscopic features are too distinctive to have been missed. Use of hematoxylin and eosin stains shows a granular and floccular acidophilic material filling large groups of alveoli. Small acicular spaces are scattered

throughout this acidophilic substance. This acidophilic substance, referred to as "proteinaceous" material, is periodic acid-Schiff positive.

This alveoli-filling material may originate from the large mononuclear cells in the walls of alveoli, the so-called "septal cells," which slough into the alveoli and undergo necrosis.[90] If this is so, the material may be related to the neonatal pulmonary hyaline membrane, as Barter and Maddison[5] believe that this membrane originates from necrosis of epithelial cells in the respiratory bronchioles. Other investigators think that this alveolar-filling material is a transudate.

Etiology

Taxay and coworkers,[104] reporting a case of pulmonary alveolar microlithiasis and pulmonary alveolar proteinosis, said:

"We believe that although alveolar proteinosis, pulmonary corpora amylacea and pulmonary alveolar microlithiasis may be different diseases, the evidence to substantiate their separation is far from conclusive. We suggest that pulmonary alveolar microlithiasis and pulmonary alveolar proteinosis represent inherent defects of the pulmonary alveolar capillaries, so that in response to normally encountered inhalants a flux of plasma ultra-filtrate occurs and, following contact with ambient air, resorption becomes impossible owing to physicochemical change . . . [and] calcification may occur."

In the rather complicated case reported by Williams and coworkers[106] calcification of pulmonary alveolar contents had occurred. "The alveolar walls," they said, "showed moderate patchy fibrosis, which in general contained no inflammatory cells. In a few areas the alveolar contents had calcified *in toto,* apparently having shrunk to form a group of calcified, often laminated bodies embedded in dense fibrous tissue."

The chest x-ray film of a patient with pulmonary alveolar proteinosis frequently resembles that seen in acuate pulmonary edema. However, comparisons of the pathologic features of these diseases indicate that they are separate entities. Mendenhall and coworkers,[68] after reviewing 532 cases of pulmonary edema, concluded that pulmonary edema was not related to pulmonary alveolar proteinosis.

There is another peculiar lung disease called pneumocystis carinii pneumonia, or interstitial plasma-cell pneumonia, which resembles pulmonary alveolar proteinosis radiographically and pathologically. In the pneumocystis infection the alveolar contents are said to be reticular and foamy. While only a few cases of pneumocystis pneumonitis have been reported in this country,* it is said to be quite common in Europe. The cause of this lethal pneumonia is thought to be a small, round organism which stains positively with silver chromate and is confined to the alveolar spaces. Since this "organism" has not been cultured nor the disease transmitted to laboratory animals, its relationship to the disease is not clear.

The difficulty of distinction is illustrated by noting that Dick and coworkers,[26] in 1957, reported on two patients with "pneumocystis carinii infection" who later were reported by Rosen[90] as cases 19 and 20 in his collected series of 27 patients with pulmonary alveolar proteinosis. The roentgen findings in pneumocystis carinii pneumonia have been described as a finely granular peripheral pattern distributed throughout both lung fields, not unlike the pattern of peripheral atelectasis seen in hyaline membrane disease.[80] While pneumocystis infection is reported to be a disease of premature infants, a few adults have been reported as having it. Hendry and Patrick[44] reported 13 cases of pneumocystis carinii pneumonia occurring in patients seriously ill with other diseases such as leukemia and lymphoma.

Reports of Two Cases

CASE 1. A 52-year-old white man, a printer, first noted onset of shortage of breath in July 1961. It rapidly increased in severity and within three months the patient had dyspnea, with coughing, on slight exertion. His main complaint was, "I have to pant to breathe." He had been raising small hard "chunks" of sputum. Until the present, the patient had always been healthy. He had lived in Tampa, Florida, until moving to Sacramento in 1947. He had been a printer all his adult life and had had no known exposure to toxic fumes or dust.

On physical examination the patient appeared to be healthy and well developed. He was slightly obese. The only abnormalities noted were dullness and diminished breath sounds over both lower lung fields. Rales were not prominent.

Routine small chest x-ray films on 14 October

*Reference Nos. 14, 30, 44, 50, 91.

1960 and 27 June 1961 had been reported to be normal. A 14 × 17-inch film on 11 September 1961 showed extensive bilateral infiltration, giving the lungs an opaque, hazy, slightly granular appearance (Figure 1).

No striking changes were observed on bronchoscopic examination but bronchograms showed very little patency of the lower lobes, due to a consolidation process. Cultures of the tracheo-bronchial aspirate were negative for fungi and bacilli.

On 3 October 1961 right thoracotomy was done and biopsy material was taken from the right lower lobe of the lung. Most of the right lung, with the exception of the apex of the right upper lobe, was solid and liver-like to palpation. The visceral pleural surfaces were covered with small yellow plaques. Caseous whitish-yellow exudate oozed from the cut surface of the lung.

Pathologist's Report

Microscopic examination of the lung showed that the pulmonary alveoli were distended with a slightly broken-up acidophilic debris. The debris for the most part was relatively acellular with only an occasional nucleus contained within and rarely showing globule formations of more intense acidophilia. Rare dissolved-out acicular slits were noted. The alveolar septations are reduced to mere fibrovascular remnants with focal zones exhibiting a delicate infiltration of rounded cells and anthracotic pigmentation. Occasionally seen were masses of xanthomatous type macrophages with numerous multinucleate giant cells usually against a pulmonary trabeculation; small giant cells of six nuclei were occasionally plastered against a septal wall.

Pathological diagnosis: pulmonary alveolar proteinosis.

Postoperatively the patient did well until the third day, when fever to 39.4°C (103°F) developed. Cultures of the sputum revealed no specific pathogen. One suture became infected with staphylococci. The infection cleared rapidly with erythromycin therapy. In spite of active therapy including prednisolone intravenously, potassium iodide and antibiotics (no penicillin or sulfadiazine were given because of a history of allergic sensitivity to these drugs) the condition of the patient continued to worsen and he died 22 October 1961, due to anoxia. At autopsy consolidation of both lungs was noted. The lower lobe of the right lung was extensively destroyed by a suppurative reaction.

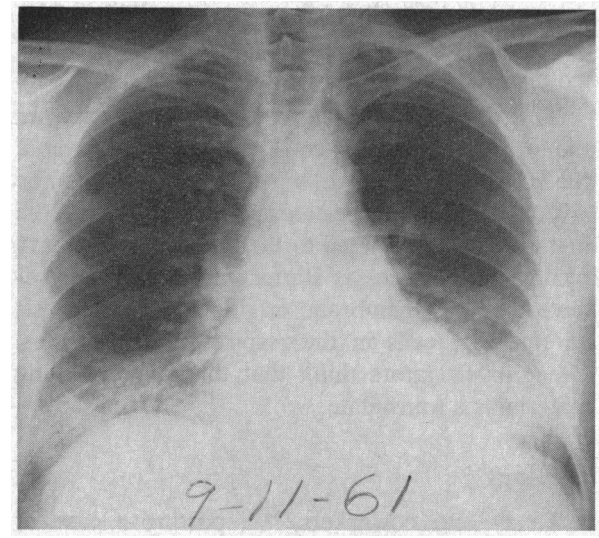

Figure 1.—Chest x-ray of Case 1 showing the characteristic changes in the lungs of patients with pulmonary alveolar proteinosis; the involvement is typically lower lobe and bilateral.

Microscopically extensive pulmonary alveolar proteinosis was noted in both lungs. In some areas microabscesses and macroabscesses were seen. Cultures from the abscess cavities yielded *Nocardia asteroides.*

CASE 2. A 40-year-old white male salesman noted the onset of a dry cough, tightness in the chest, with pain in the left side of the chest and the left shoulder, in June 1963. He sought medical attention in September 1963. At that time he also complained of severe nervousness and admitted excessive intake of alcohol. He was disturbed by marital problems. The patient knew of no known exposure to toxic dusts or fumes except that he was a heavy smoker of cigarettes. He had noticed rasping voice and change in tonal quality over the preceding six months.

Except for those mentioned by the patient, no abnormalities were noted on physical examination. Results of extensive laboratory investigation were all within normal limits. No abnormalities were seen bronchoscopically and cultures of aspirated tracheo-bronchial secretions grew no pathogens. An x-ray film of the chest showed patchy and linear densities in both lungs (Figure 2). Bronchograms were within normal limits.

Left thoracotomy and excision of biopsy material from the lower lobe of the left lung were performed 21 September 1963. On palpation, diffuse nodulation within the substance of both lobes of the left lung was noted.

Pathologist's Report

Microscopic study of the excised lung tissue showed an acidophilic material ranging from homogeneous to finely granular intermingled with still identifiable red blood cells filling clusters of alveoli and occasionally alveolar ducts and terminal bronchioles.

Pathological diagnosis: pulmonary alveolar proteinosis.

The patient recovered from the operation without difficulty and at last report, 18 months later, still had extensive pulmonary disease as shown by x-ray films of the chest.

Analysis of Reported Cases

Up to the first of 1964, 93 cases of pulmonary alveolar proteinosis had been reported, including the two cases herein. From correspondence with the authors of all the reports, it was learned that 20 of the patients were known to be alive at the beginning of 1964, 37 dead and 36 lost to follow-up. Seventy-four of the 93 patients were males and 19 females. Seventy-seven were white, 12 were Negroes, three were Japanese and one Chinese. Fifty-eight of the 93 patients were between 30 and 50 years of age. The youngest was two and a half years old, the oldest 72.

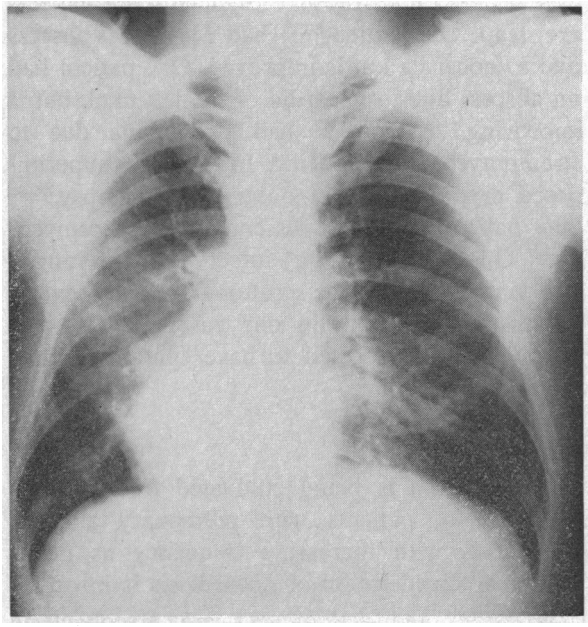

Figure 2.—Chest x-ray of Case 2. Infiltration is present in both lungs but is more pronounced in the left mid-lung field. Diagnosis of pulmonary alveolar proteinosis by left lung biopsy on 21 September 1963. Patient alive and well as of 22 April 1966.

The patients were of a wide variety of occupations, and there was no consistent history of extraordinary exposure to fumes or dusts.

Symptomatology

Furst and coworkers[38] reported the case of a patient with extensive pulmonary alveolar proteinosis who had no symptoms; evidence of the disease was noted on routine x-ray examination of the chest. It was thought that the disease had probably been present for at least four years but without causing symptoms. Similarly Oka and coworkers[74] reported the case of an asymptomatic 19-year-old girl with extensive disease seen on a routine x-ray film of the chest.

More commonly the symptoms which cause the patient to seek the aid of a physician are those due to pulmonary insufficiency—namely, dyspnea on exertion, cough, fatigue and, less commonly, cyanosis. Frequently a history will be given of recurrent attacks of severe upper respiratory tract infection or pneumonia. The patient may present with chills, fever, cough, blood-flecked sputum and pain in the chest. The more seriously ill patients will have dyspnea at rest, cyanosis, clubbing of digits and hemoptysis. The patient may volunteer that he has been coughing up small "chunks" of material.

Physical Examination

The patient is usually a well developed, well appearing white man between 30 and 50 years of age who may present few abnormalities. Breath sounds over the lower lung fields may be diminished, with dullness and a few rales present. The more seriously ill patients have dyspnea at rest, cough, cyanosis and clubbing of the terminal phalanges.

Laboratory Work

Most patients with pulmonary alveolar proteinosis have been extensively investigated. Most important in the investigation are roentgenograms of the chest and cultures of the sputum.

The frequent occurrence of fungus infections and pulmonary alveolar proteinosis indicates the need for searching the tracheo-bronchial aspirate and any other suspected area for organisms. Usually, moderate polycythemia exists, due to the stimulating influence of hypoxia. With infection the leukocyte count rises as expected.

Roentgenographic Examination of the Chest

Features on x-ray films of the chest in pulmonary alveolar proteinosis are more or less characteristic. As seen on roentgenograms, both lower lung fields are involved. Sometimes the lesions have been confused with acute pulmonary edema, which they resemble radiographically. Roentgenologists have variously described the lesions as, "a granular lower lobe infiltrate, bilateral," "a fine, diffuse, perihilar, radiating feathery or vaguely nodular soft density resembling in its butterfly distribution the pattern seen in severe pulmonary edema," and "diffuse linear strands radiating from both hilar areas, bilateral."

On the other hand the lungs may be severely involved and yet appear to be normal roentgenographically.[12,13] This is especially deceiving when on x-ray films the lesion may appear to clear. Burbank and coworkers[13] reported a patient with pulmonary alveolar proteinosis and nocardiosis who was apparently cured of both diseases. The patient died of mesothelioma. Roentgenograms before death showed clear lung fields; also biopsy of a small specimen of the lung revealed no proteinosis, but at autopsy 10 days later extensive pulmonary alveolar proteinosis was found in both lungs.[12]

Repeated x-ray films may show no change for years, or there may appear to be clearing, or it may get worse. So far, complete resolution of the pulmonary disease has not been proved in any case.

Diagnosis

The diagnosis has been established by lung biopsy or at autopsy, with the following exceptions: one patient with a typical history and roentgenographic findings did not have biopsy, but study of "white and chunky" sputum was thought to be indicative of pulmonary alveolar proteinosis; one patient had biopsy of a specimen obtained with a Vim-Silverman needle; two patients reported by Rosen and coworkers did not have lung biopsy but did have roentgenograms typical of the disease.

The possibility of error if the biopsy specimen is too small has already been illustrated in the previously mentioned case reported by Burbank.

It was pointed out by Lundberg[58a] that, due to the presence of mucopolysaccharides in normal and abnormal tissue, colloidal-iron stain of coughed-up material is not diagnostic for pulmonary alveolar proteinosis.

Analysis of Patients Who Have Died

Of 37 patients with pulmonary alveolar proteinosis who are known to be dead, 19 had complicating diseases and the remaining 18 died of the hypoxic effects of pulmonary alveolar proteinosis. Eight of these patients had superimposed nocardiosis and four had cerebral abscesses. The duration of the disease varied from three months to 17 years.

Analysis of Patients Still Alive

Twenty patients are known to be alive with pulmonary alveolar proteinosis. All of them still have evidence of the disease with the possible exception of one patient who is said to have no pulmonary lesions visible on x-ray films of the chest.[48,88,94] One patient had had the disease for 18 months at the time of this report and the others for over four years. One patient[64,65] has had pulmonary alveolar proteinosis for 17 years. No specific treatment has been found to be effective.

Pulmonary Alveolar Proteinosis and Fungus Infection

Ten patients with pulmonary alveolar proteinosis also had nocardiosis.* Eight of these patients are dead. One patient[20,21] had a cerebral abscess due to nocardia but is improved. One patient had an abscess due to nocardia of the left flank but is improving.[1,46] One[61,62] had pneumonia due to streptomyces but recovered. In two cases superimposed cryptoccosis was observed at autopsy.[56,90] One patient died with disseminated mucormycosis.[47] One had aspergillus infection of the lung.[27] A draining lesion of the scrotum developed several months before death in one case.[70,92] Two patients[11,83] were reported to have sputum positive for acid-fast bacilli.

Nocardiosis

As nocardia is being cultivated from various infections of patients with pulmonary alveolar proteinosis with increasing frequency as noted above, a consideration of nocardiosis is in order.

Nocardia and actinomyces are mycobacteria and members of the order of actinomycetalis. Nocardia asteroides, the causative organism in most

*Reference Nos. 1, 3, 13, 16, 20, 21, 84, 85, 90, 103.

cases of nocardiosis, is an aerobic, Gram-positive, branching filamentous fungous, variably acid-fast.

Over 213 cases of nocardiosis have been reported.†

Nocardiosis may run a rapidly fulminating fatal course or may be prolonged and chronic. Any tissue may be affected but the commonest site of infection is the lung. Next in order are the brain, the skin and subcutaneous tissues, and the pleura. Nocardiosis may simulate many other diseases[42a] or may occur coincident with other diseases.

Raich and coworkers[84] reported nocardiosis occurring with sarcoidosis, pulmonary tuberculosis and cancer of the lung. Stein and Estrellado[101a] reported the fourth case of pulmonary tuberculosis and nocardiosis. Freese and coworkers[36] reported 11 patients with nocardiosis. Nine were cured by sulfonamide therapy and two who had brain abscess, died. Webster[105a] reported 10 cases of pulmonary nocardiosis. Hathaway and coworkers[42a] reported 14 cases, with 11 of the patients recovering. Nocardiosis was superimposed on tuberculosis in two patients, chronic lymphatic leukemia in one and generalized sarcoidosis in one. Cross and coworkers,[23] reviewing 44 cases from the files of the Armed Forces Institute of Pathology, concluded that nocardiosis was primary in 27 cases and that, in the remaining 17, other serious diseases antedated the nocardial infection.

Nocardia is not normally found in the human respiratory tract: Raich and coworkers[85] were unable to isolate any nocardia at all from 235 specimens of sputum, gastric washings and tonsils from 109 patients.

Since nocardia are easily cultured and treatment with sulfonamides is usually successful, one must keep the agent in mind particularly when dealing with pulmonary alveolar proteinosis.

For the successful treatment of a very severe case of nocardiosis with all imaginable complications, one should refer to the report by Pellegrin and Henderson.[78] This case was also unusual in that the patient was moribund when massive doses of penicillin saved her life. Sulfonamides were not effective in that case.

Treatment

Patients with pulmonary alveolar proteinosis have been treated with numerous agents but no specific agent can be said to have been found. Ramirez and coworkers[86] have attracted some attention by the use of "segmental bronchial flooding," in which saline solution heparin or other agents are introduced into certain areas of the lung through a small indwelling catheter which has been passed through the larynx.

Several patients have had trypsin administered in oxygen aerosal by intermittent positive pressure, but most of the patients with pulmonary alveolar proteinosis who are still alive have had no special therapy.

The patient who has had pulmonary alveolar proteinosis for the longest time, 17 years, is a Chinese who is now 69 years old. This patient was reported by McDowell and coworkers[65] as having had "pneumonia" in 1947 and subsequently required numerous periods in hospital. In November 1952 he was again put in hospital with progressive dyspnea, cyanosis and almost complete opacification of both lungs on x-ray films of the chest. A lung biopsy in 1953 established the diagnosis of pulmonary alveolar proteinosis. After this the patient improved and has remained well. As of December 1963 the patient was reported by McDowell to be working hard in his green-grocery business. McDowell believed that massive doses of potassium iodide which the patient accidentally received in 1953, may have contributed to his recovery.

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†Reference Nos. 4a, 15a, 23, 36, 42a, 77, 78, 84, 98, 101a, 105a.

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